Editorials

Progress in Adult Acute Lymphoblastic Leukemia

ELSEWHERE IN this issue of THE WESTERN JOURNAL OF MEDICINE, Levitt and Lee provide an excellent review of the pathogenesis and treatment of acute lymphoblastic leukemia (ALL) in adults.[1] As noted by the authors, there has been considerable progress in our understanding of the nature of the malignant cell in ALL. The challenge we now face is the more difficult task of learning how to use this information.

One area where enormous progress has been made is in our understanding of the molecular events underlying adult ALL. In more than 90% of cases of ALL, a clonal chromosomal abnormality can be identified.[2] In about 25% of cases, the abnormality is one of numbers, with 20% of patients being hyperdiploid and 5% being hypodiploid. But more commonly, the abnormality is a specific chromosomal translocation. Such translocations are thought either to generate a novel gene (an oncogene) whose protein product acts on the host cell to induce characteristics of malignancy, or to cause a loss or an inactivation of genes whose proteins normally suppress cancer. In adult ALL, the genes involved in most of the commonly seen chromosomal translocations have now been identified.

The most common translocation found in adult ALL is the Philadelphia chromosome (Ph), t(9;22)(q34;q11). The Ph chromosome is formed by a translocation that fuses part of the *bcr* gene on chromosome 22 with sequences upstream of the c-*abl* proto-oncogene on chromosome 9. By traditional cytogenetic analysis, about 20% of adult ALL patients are Ph-positive. It has come as something of a surprise to find that at least an additional 10% of patients, Ph-negative by conventional cytogenetics, have *bcr-abl* rearrangements detectable with the use of polymerase chain reaction (PCR) assays.[3] This discrepancy is likely due either to the poor growth of lymphoid blasts, making conventional cytogenetic analysis difficult, or unusual "microscopic" translocations or "one-way" insertions of the *abl* gene into the *bcr* gene. The breaks in chromosome 22 occur in two limited regions, called the major and minor break-point cluster regions (BCRs). In chronic myelogenous leukemia, virtually all breaks are at the major BCR, giving rise to a p210 *bcr-abl* protein, but in patients with ALL, about 50% of cases occur in the minor BCR, giving rise to a p190 *bcr-abl* protein, the other 50% occurring at the major BCR. Despite the fact that we understand a great deal about t(9;22) in adult ALL, the only established therapeutic use of this knowledge to date has been as an important prognostic factor. When compared with Ph-negative adult ALL patients, patients with Ph-positive ALL have modestly lower complete remission rates and far shorter remission durations and, therefore, should be considered for allogeneic transplantation early in their disease course. Although results are still preliminary, patients with the minor break point may have a somewhat more aggressive disease than those with major break points. Polymerase chain reaction-based assays can be used to detect occult residual disease, but no clear clinical use of this approach has yet emerged.

The story for other translocations seen in adult ALL is similar. We now know the gene partners in most of these translocations, but we have as yet made little clinical use of the information. The identification of these translocations has in some cases provided us with additional prognostic information, and in those cases where specific primers are developed, a sensitive assay for minimal residual disease exists, but novel therapies have yet to emerge based on these studies. Other molecular abnormalities seen in adult ALL include mutations of N-*ras* in 10% to 25% of cases and mutations in Rb1 in a like percentage of patients. Mutations in p53 are rare in most forms of ALL, but common in patients with Burkitt's leukemia.

In addition to our increased knowledge of the molecular abnormalities seen in ALL, the immunophenotypic classification of adult ALL continues to be refined. This classification is based on increased knowledge about how normal cells acquire cell-surface antigens during development and information on the progression of events surrounding the rearrangements of immunoglobulin and T cell-receptor genes in normal cells. B-lineage ALL is now subdivided into at least four subtypes, including early pre-B common ALL antigen (CALLA)-positive and -negative ALL, pre-B ALL (note the absence of the "early"), and B-cell ALL. About 25% of cases are T-lineage ALL, including pre-T ALL and T-cell ALL. Cells from about 25% of cases of adult ALL coexpress the myeloid antigens CD13 or CD14 (or both). Similar to recent knowledge in the molecular events of ALL, advances in immunophenotyping have been used chiefly to refine the prognosis. Patients with T-cell and CALLA-positive, early pre-B ALL tend to do the best, whereas patients with pre-T ALL, CALLA-negative, early pre-B ALL, and those patients whose blasts coexpress myeloid antigens tend to do worse.[4,5]

Although the increased molecular and immunophenotypic information concerning adult ALL has not yet provided new therapies that can be considered established, a number of attempts are under way to try to make use of this information. The following examples are noted here:

- In those cases wherein the precise translocation leading to malignancy is known, it may be possible to silence the abnormal gene using antisense constructs or by eliminating the abnormal sequence using ribozymes.[6] Although antisense and ribozyme constructs work in vitro when a small number of cells are targeted, it is less certain whether the hurdle of having to deliver such therapy to every cell in vivo can be overcome. Thus, initial trials are looking at these agents as a way of treating marrow in vitro before autologous transplantation.

• In addition to silencing or eliminating the genetic defect in ALL, attempts are being made to use the defect to gain a therapeutic advantage. After exposure to DNA-damaging agents, normal cells undergo cell cycle arrest in either G1/S or G2/M, using the extra time to repair damage before progressing through the cell cycle. In many leukemia and lymphoma cell lines, the loss of p53 function leads to an inability to undergo cell cycle arrest or to trigger apoptosis, and thus these cells are relatively resistant to irradiation, but also rely entirely on G2/M arrest for DNA repair. Studies have recently shown that, at least in vitro, treatment during or after irradiation with agents that abolish G2/M arrest increase radiation sensitivity selectively in p53 mutant cells that rely on G2/M arrest without increasing the sensitivity of normal cells that can arrest in G1/S.[7,8]

• The immunophenotype of ALL may provide a target for therapy. Antibodies that recognize the specific antigens expressed by ALL can be used to target toxins to the leukemic cells. For example, human pre-B leukemia growing in immunodeficient mice has been successfully treated by targeting a tyrosine kinase inhibitor (genistein) to the B-cell–specific receptor CD19.[9] A slightly different approach has been undertaken in patients undergoing marrow transplantation for ALL. In these studies, antibodies against CD45, an antigen found on most hematopoietic cells, have been used to target iodine I 131 to sites of leukemia and normal marrow to more reliably eradicate the disease before marrow transplantation.[10]

• Following allogeneic transplantation for ALL, the risk of relapse is far less in patients in whom acute or chronic graft-versus-host disease develops than in identical twins or those free of graft-versus-host disease.[11] Studies in animals and humans have shown that the most likely explanation for this phenomenon is that cytotoxic T cells arising from the transplanted marrow recognize and react with HLA-minor antigens expressed either uniquely by leukemic cells (tumor-specific antigens) or shared by other cells of the same lineage (tumor-associated antigens). Studies under way at present are directed at identifying and isolating the T cells responsible for this outcome and their targets. Having the cells in hand would allow for their expansion and reinfusion, providing a form of tumor-specific adoptive immunotherapy. Identifying the T-cell target might lead to the generation of effective antitumor vaccines.

Although these approaches represent exciting new opportunities, it should be acknowledged that most of the advances made in the treatment of adult ALL have been the result of far more conventional sorts of studies. Based on these studies, 40% to 50% of adults with ALL can expect to be cured with the use of currently available therapies. Further progress will likely require both a continuation of conventional studies that look at new drug combinations, doses, and sequences and the introduction of some of the new approaches described earlier. To this end, it should also be remembered that ALL is a relatively uncommon disease and is, in fact, the least common of the four major leukemia categories. Thus, physicians should make every effort to include patients in established clinical trials to make sure that progress continues.

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FREDERICK R. APPELBAUM, MD
Clinical Research Division
Fred Hutchinson Cancer Research Center
and University of Washington
School of Medicine
Seattle, Washington

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